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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,155	04/03/2001	Ariel Ruiz i Altaba	1049-1-008 N CON	2618

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EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 11/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,155	ALTABA, ARIEL RUIZ I	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The election filed August 29, 2002 (Paper No. 14) in response to the Office Action of July 2, 2002 is acknowledged and has been entered. Applicant has elected Group VII (Claim 9) without traverse.

Claims 1-9 are pending.

Claims 1-8 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claim 9 is currently under consideration.

Specification

The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the priority status of the present application, for example:

This application is a continuation of U.S. application No. 09/102,491, filed June 22, 1998, now U.S. Patent No. 6,238,876 which claims benefit to provisional application 60/050,286, filed June 20, 1997, now abandoned.

The specification is further objected to because there is no brief description of Figure 7, which appears to show expression of Gli1, Gli3, Shh and S17 in BCC and SCC by RT-PCR.

The specification is further objected to on page 13, lines 13-21 for improper disclosure of nucleotide sequences without a respective sequence identifier, i.e. a SEQ ID NOs:. Hence, the

disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). (See attached Notice to Comply at the end of this Action)

Claim Objections

Claim 9 is objected to, in part, for reciting "or a specific binding partner" which reads on a non-elected invention as per the restriction requirement in Paper No. 14, page 2. This objection can be obviated by canceling the non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. For example, claim 9 recites "inhibitors of the expression and activity of Gli1, their complements or fragments thereof, and mixtures thereof" as therapeutically effective materials. However, the specification does not distinctly define what is included or excluded as complements or fragments or mixtures thereof. For example, the specification teaches (page 2,

line 34) that such therapeutic agents may include small molecules and ligands. However, it is not clear what constitutes a complement of a ligand (or small molecule) or a fragment of ligand. Moreover, it is not clear what the mixture thereof comprises. Complements and fragments? Hence, the metes and bounds of the claim cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention as claimed.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claim is drawn to a pharmaceutical composition for the treatment of cellular debilitations, derangements and/or dysfunctions and/or disease states in mammals caused by the development and presence of sporadic basal cell carcinoma, comprising a therapeutically effective amount of a material selected from the group consisting of inhibitors of the expression

and activity of Gli1, their complements or fragments thereof, and mixtures thereof, and a pharmaceutically acceptable carrier thereof.

The specification teaches (page 2, lines 30-35) that the invention includes the development of therapeutic agents that are capable of controlling the expression and/or activity/function and expression of Gli1, and are thereby able to inhibit the development and/or treat sporadic basal cell carcinoma in animals, particularly humans. Thus, the disclosure broadly encompasses a method of treating basal cell carcinoma in animals. The specification further teaches that such agents may include small molecules, ligands, and other agents that would function as Gil1 antagonists or would otherwise interrupt Gli1 expression and activity (top of page 3).

However, with regards to the prevention and or treatment of diseased states, cellular debilitations, cellular derangements or dysfunctions caused by the development and presence of sporadic basal cell carcinoma, the specification provides insufficient guidance and objective evidence that such pharmaceutical compositions comprising inhibitors of the expression and activity of Gli1, their complements or fragments thereof, and mixtures thereof would predictably invoke a therapeutic response, especially with regards to the prevention or treatment of sporadic basal cell carcinoma. Furthermore, the specification provides no guidance or objective evidence of any clinically significant change in the S phase activity of a target cellular mass, or other feature of pathology such as for example, elevated blood pressure, fever, or white cell count as may attend its presence and activity.

In general, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-

cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, as drawn to peptides, Bellone *et al.* (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Furthermore, with regards to the prevention of a targeted cell mass, e.g. a tumor, reasonable guidance relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories.

The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. As, such the specification is void of any guidance related to the administrative prevention of a "clinically significant change in the S phase activity of a target cell mass" and is essentially void of a specific and well-defined pharmaceutical composition since the composition broadly encompasses any and all agents known to man including, but not limited to, ligands and small molecules.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the pharmaceutical compositions as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Yamada *et al.* (US Patent No. 5,247,070, 1993).

Because of the open and indefinite nature of the claim language, it is assumed for examination purposes that "material selected from the group consisting of inhibitors of the expression and activity of Gli1, their complements or fragments thereof, and mixtures thereof" broadly encompasses any pharmaceutical composition comprising any fragment or complement of a polypeptide or polynucleotide (or any small molecule or ligand) as previously described in the rejection of claim 9 under USC 112 2nd paragraph.

The claim is drawn to a pharmaceutical composition for the treatment of cellular debilitations, derangements and/or dysfunctions and/or disease states in mammals caused by the development and presence of sporadic basal cell carcinoma, comprising a therapeutically effective amount of a material selected from the group consisting of inhibitors of the expression and activity of Gli1, their complements or fragments thereof, and mixtures thereof, and a pharmaceutically acceptable carrier thereof.

Yamada *et al.* teach a pharmaceutical composition comprising a therapeutically effective amount of a material selected from the group consisting of various polypeptides and fragments thereof and a pharmaceutically acceptable carrier (column 48). Although the reference does not specifically teach that the claimed composition is useful for the treatment of cellular debilitations, derangements and/or dysfunctions and/or disease states in mammals caused by the development and presence of sporadic basal cell carcinoma, the claims read on the active ingredients *per se*, which *include* polypeptide compositions. The intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to

patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
November 8, 2002